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IMMUNE SERA AND CERTAIN BIOLOGICAL PROBLEMS[1]

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Mr. President, Members of the Academy of Medicine of Cincinnati: I am deeply appreciative of the honor conferred upon me by the invitation to address this medical society. Although my own researches have lain outside the conventional limits of medicine, it happens that several of them have crossed the border lines of this science and have thereby quickened the naturally keen interest in the scientific aspects of medicine that I have always entertained. In my present researches, indeed, I have borrowed some of my most important tools and ideas from the field of immunological studies and discoveries, made in the main by medical researchers. The luxuriant growth of literature in recent years on immunity, antitoxins, cytotoxins, bacteriolysins, hemolysins, opsonins, precipitins, agglutinins, anaphylaxis, and what not, is known to you all. Naturally, the brilliant series of practical applications of this new knowledge in diagnosis, prophylaxis and therapeutics, stimulated every medical investigator to redoubled effort until the field has become almost exclusively the domain of the bacteriologist and the pathologist.

It may seem presumptuous of me, a biologist, to step outside the traditional bounds of my science and to come, carrying coals to Newcastle as it were, in recounting to you various facts long since learned by physicians—

[1] An address delivered before the Academy of Medicine of Cincinnati.

facts which lie at the very foundation of modern medical theory and practice. I offer my apology in advance for the lack of novelty in much of what I shall say. My only justification is that a reconsideration of such familiar knowledge gives one a good running start, so to speak, for a leap into less known realms; realms of great interest to the embryologist, the cytologist, the student of heredity and of evolution; regions in which lie hidden the secrets of all life and form, of hereditary transmission, and of its converse, variation.

It is clear that the phenomena which constitute the field of immunology, although to-day viewed mainly from the standpoint of infection and immunity, all have broader biological aspects. They must in last analysis be but heightened or specialized reactions of the fundamental processes which underlie all life phenomena. They are but one of the many expressions of that delicately balanced stereochemical system we call protoplasm, and they are inextricably interwoven in the ebb and flow of metabolism, with such fundamental biologic processes as growth, reproduction, irritability and adaptation.

The physiologically minded biologist also inevitably suspects close relationship between the reactions described by the serologist and those manifested normally in a living animal by that wonderful system of chemical messengers or internal secretions, the hormones and chalones, which, independently of the nervous reflex, can stimulate or inhibit the activity of some organ in a part of the body far distant from the source of the secretion itself, and which undoubtedly play an important part in development. There seems no reason to doubt that both hormones and antibodies, for example, represent complexes of atoms which were originally parts of body-cells concerned in the normal metabolic processes. One is extruded into the body fluids under the influence of a usual and therefore normal stimulus, the other is the product of an accidental stimulus resulting from disease or other unusual condition.

In any event this whole field of endocrinology and serology stands as a perpetual challenge to the experimental biologist. Some sixteen years ago Nuttall published his remarkable series of studies on "Blood Immunity and Blood Relationship" in which he reported the results of his examination of some nine hundred different samples of blood from various kinds of animals. He demonstrated that by the precipitin test a differential scale of actual blood relationships among animals can be established. As you doubtless recall, when an animal of one species is injected parenterally with successive doses of blood-serum of another species over a period of a few weeks, the blood-serum of the injected animal acquires the ability to form a precipitate with that of the alien species when the two sera are mixed. When the reaction is carried on in vitro, even in dilute solutions, the cloudiness and ultimate flocculation which results are easily seen. If, for example, a rabbit is thus repeatedly injected with human blood its blood-serum when mixed with slightly diluted human blood-serum in vitro will almost instantly yield a noticeable precipitate, though a control mixture of human blood-serum and the blood-serum of an untreated rabbit will remain clear. The ingredient which has been engendered in the serum of the rabbit is termed a *precipitin,* and the foreign serum which was injected—human blood-serum in this case—is called the *antigen,* or more specifically, the *precipitinogen.* It is known that not only blood-serum, but also milk, globulins, various albumins and bacterial products—in fact probably any foreign protein—may serve as antigen for the formation of precipitins. The reaction is not absolutely specific in low dilutions since species of animals related to the one from which the antigen was taken will also, though in less degree, give the effect. Closeness of relationship is determined by finding the dilution in which the serum to be tested will react. For instance, Nuttall found that when rabbit serum which has been sensitized against human serum is mixed with the moderately di-

luted sera of man, apes and monkeys, respectively, it reacts to all, though in a varying degree. When mixed with more highly diluted sera from such animals, it forms a precipitate only with the serum of man and the manlike apes (chimpanzee, orang-outang, gorilla), the chimpanzee standing nearest to man. Absolute specificity may be obtained if the antigen is sufficiently diluted. On the basis of extensive experience, Uhlenhuth sets a dilution of antigen of 1 to 1,000 as a standard beyond which no precipitation will occur except with the specific antigen employed in the sensitization.

Thus the precipitin test became useful to the zoologist in discriminating between different species, and it may prove of importance in establishing the taxonomic position of new forms, or in confirming or changing the classification of groups already known. The delicacy of the test is remarkable. A properly sensitized serum may give a reaction with blood diluted 20,000 or even 50,000 times. Sera have been obtained, indeed, in which specific antigen could be detected in a dilution of 100,000. When one recalls that ordinary chemical tests cease to give detectable reactions in blood diluted 1,000 times, he can appreciate the value of these physiological methods of measurement to the biologist. They apprise him of species differences between the proteins of various animals which can not be determined by any known chemical methods.

The value of the precipitin test in forensic medicine, in determining the nature of blood stains on clothing, weapons or other objects, is well known to all of you, as is doubtless their utilization in meat inspection, such as for the detection of horse-flesh or dog-flesh in sausages or other chopped meats, and in various other types of adulteration.

One thing that interests the biologists greatly in the precipitin reactions is the fact of so-called "species specificity"—the fact that blood sensitized against one tissue of a given foreign species will react with extracts of

the other tissues of that species. Thus the blood-serum of a rabbit which has been treated with sheep blood-serum will form a precipitate not only with the sheep serum, but with the extracts of sheep muscle, sheep liver, sheep spleen, and other organs of the sheep. This clearly implies that each species of animal possesses something in common throughout all its tissue proteins, something peculiar to that particular species which in last analysis must be resolved into a problem of its general metabolism and stereochemistry. This does not mean that organs may not also have protein complexes peculiar to themselves. Indeed, it is an established fact that they do. And what is more, some of these organal peculiarities may be common to various species. For example, the fact of "organ specificity" has been established for the crystalline lens. According to Uhlenhuth, immunization with crystalline lens of a given species of animal yields a precipitin which reacts with the lens proteins of many different species of animals. Von Dungern and others have secured similar results with proteins derived from the testis. Confirmatory evidence of this fact that a type of specificity attaches to the nature of the organ itself, irrespective of species, has also been established by means of the reaction of anaphylaxis.

The precipitin reactions, then, teach the biologist that in the chemistry of the general proteins of a given animal, there are certain fundamental similarities, also that there are constant species differences between the homologous proteins of different species of animals, and lastly, that some proteins, in certain highly specialized organs at least, though existing in different species, possess similar chemical characteristics.

These and related facts when considered in conjunction with such as those of Reichert and Brown regarding the stereochemical correspondences in the living matter of allied species as demonstrated in the crystallography of their hemoglobins, or the studies of Reichert on the relations of the starches and tissues of parent-stocks to those

of hybrid-stocks in plants—such facts taken all together are gradually constructing for the biologist a rational biochemic basis for the study of the fundamental processes operative in metabolism, heredity and evolution.

But let us now turn our attention to another type of serological reactions, those concerned with the cytotoxins or cytolysins. You doubtless all recall the well-known experiments of Bordet, in 1898, in which he found that the blood of guinea-pigs which have been repeatedly injected with the red blood corpuscles of the rabbit, acquire the property of rapidly dissolving rabbit corpuscles. This is the familiar phenomenon of *hemolysis,* and the substance in the blood-serum of the guinea-pig which brings about solution of the red corpuscles of the rabbit is termed a *hemolysin.* Bordet showed further that this enhanced solvent action of the serum of animals treated with the red blood cells of a different species exists only for the kind of red corpuscles used as antigen, not for those of other species of animals. Exceptions occur, though in the main the reaction is specific. The similar facts regarding bacteriolysins, which are now commonplaces of every-day medicine, had been established a year earlier.

It was soon discovered that other materials such as leucocytes, nervous tissue, spermatozoa and crystalline lens, when injected into the blood of a foreign species will form lytic or toxic substances more or less specific for the antigen used in the immunizing process. While it is probable that none of such cytotoxins or cytolysins acts only upon its own antigen—all studied so far have been found to be somewhat hemolytic—the important fact, for our present purposes, is that although a particular cytolytic serum may affect some other tissues, it vigorously attacks the special tissue used as antigen.

This fact, when fully grasped, suggests inevitably to the biologist, or at least to the investigator interested in the mechanism of heredity and variation, queries such as the following: if a special serum can thus be constructed

which will single out and destroy a certain element of an adult organism, is it not possible that there is sufficient constitutional identity between the mature substance of that element and its representatives in the germ-cell that they too will be influenced? Is this not a way of getting at the old yet ever new problem of the inheritance of body acquirements, or at least of breaking in on the germ? Is it not possible to secure selective action on certain parts of the developing embryo and thus shed some light on the genesis of congenital abnormalities? And by using the cytolytic and other immunologic methods may not additional knowledge be gained concerning the relations of mother and fetus?

Of this series of problems the one which tantalizes the biologist most of all, perhaps, is that concerned with the possible hereditary transmission of characters acquired directly by the body of a parent. As you know, this has been a bone of contention for many years. The so-called Neo-Lamarckians follow, at least in a modified form, the teachings of Lamarck to the effect that such "acquired characters" are or may be inherited; the other school, often called Neo-Darwinians, strenuously deny such inheritance, and assert that the sole font of specific change lies in the germplasm. According to them any new inheritable feature which appears first arises in the germ and only finds somatic expression when this germ develops into a body.

How important he considered the correct solution of this problem is shown in the following statement of Herbert Spencer. He said: "Concerning the width and depth of the effects which the acceptance or non-acceptance of one or the other of these hypotheses must have on our views of life, the question, Which of them is true? demands beyond all other questions whatever the attention of scientific men. A grave responsibility rests on biologists in respect of the general question, since wrong answers lead, among other effects, to wrong belief about social affairs and to disastrous social actions."

Lamarckism at the present time, among American biologists, has all but disappeared. Some palæontologists, who in reading the records of the past find that whenever new conditions for existence occurred, new forms of life admirably adapted to those conditions appeared, are prone to believe that the environment has in some way directly molded these new inhabitants to its bounds. Since this performance has occurred again and again, they are a bit skeptical of the selectionist tenant that each occasion has had to await, not only the accidental occurrence of a favorable germinal variation, but of a host of them, which must in turn be sifted and parceled and perfected by natural selection into that adaptedness to the surroundings which characterized the organisms in question. Various students of geographical distribution also are inclined to regard the direct action of environment as instrumental in molding the fauna of a given region. In brief, those who look at the problems of evolution from wide perspective tend to postulate that altered function or environment, if long continued, in some way modifies descendants, but they don't tell us how. Those who view the problem from the standpoint of the few generations intensively studied by the geneticist, or from the germ-cell lineages of the embryologist, or the chromosomes of the cytologist, almost without exception reject the Lamarckian interpretation. And it can not be denied that the latter have an incomparable advantage in directly testing the matter, since they have their material in hand for direct observation or experimental control. So it has come about that the believer in Lamarckism, silenced if not convinced by the formidable array of negative evidence amassed against him, and still more perhaps by his own inability, from the basis of carefully controlled experiments, to cite specific examples of inherited somatic acquirements, has subsided into mute acquiescence or but faint-hearted advocacy of his theory.

The fertilized egg develops into an adult individual

through a series of cell-divisions and specializations of the new cells thus produced. During development certain cells are set apart, often very early in embryogeny, for reproducing the next generation. Thus the germ-cells and the body-cells of a given organism develop at the same time and neither is the product of the other; each alike has originated by division from the fertilized ovum. There is no necessity, therefore, for collecting samples from all parts of the body and concentrating them in germ-cells, as Darwin supposed was done, for the samples are already there, derived from the same supply that produced the parental body. They exist not in the form of such parts of an organism as are visible to us, but simply as certain ingredients which when combined in certain ways and developed in certain directions give rise to the parts in question. Sooner or later the body dies, but in the meantime one or more of the germ-cells have passed on to become expressed as new bodies and new germs. Thus a child does not inherit its characteristics from corresponding characters in the parent-body, but parent and child are alike because they are products of the same fundamental materials.

How, indeed, can a change in a brain-cell or a muscle-cell find expression in a germ which is itself a cell that possesses neither brain nor muscle? How can an influence at a distant part of the body even reach a germ-cell? How can immature young, even larvæ in some instances, produce young which ultimately come to manifest the characteristics of the adults of the species? How can recessive Mendelian unit-characters disappear, perhaps for generations, to reappear at last apparently with qualities undimmed? How, on the Lamarckian basis of use-inheritance, can the highly specialized characters of the worker-bee have originated and become perfected when the individual itself is sterile? How account for adaptive characters based on passivity, or for mutual adaptations such as may exist between plants and certain animals? These and a host of questions like them con-

front the Lamarckian when he strives to resuscitate the faith that is in him.

The opponent of Lamarckism certainly shines as a disconcerting questioner. Moreover, he is clearly correct in his contention that the idea of germinal continuity is the simpler one, and probably the only tenable one, as regards the inheritance of characters, *once they have been engendered.* But the crux of the whole problem lies in the question, where do new characters come from? According to the followers of the great biological theorist, Weismann, not only do new heritable characters originate in the germ, but a change which first appears in the body can not in any way become incorporated in the germplasm. Unquestionably, constitutional changes in a germ-cell at any time may find expression as a new or modified character in the subsequent organism which comes from this germ. But while this is an obvious fact, it gives no real explanation of the origin of the character in question, since it tells us nothing about what induced the constitutional change. Weismann regarded sexual reproduction, the intermingling of two lines of germplasm, as an important cause of germinal variation, but our modern genetical studies indicate that this is probably not true. Dual ancestry, of course, makes possible new arrangements of germinal constituents which reveal themselves in new combinations of characters, but the germinal antecedents of such combinations are unitary in nature, and there is no evidence that sexual mixture originates any new units. So the Neo-Darwinian, although highly successful in pointing out the shortcomings of Lamarck, has been little if any more successful in explaining satisfactorily how changes are *initiated* in the germ-cell. Yet it is this very item of change, of *variation,* that is the real basis of evolution.

Some selectionists glibly assert that new characters arise as the result of spontaneous changes in the germ. What is meant by this? Just what is a spontaneous change? No one has ever succeeded in telling us. And

we may suspect, though perhaps it is heresy to do so, that it is a well-sounding phrase that is the equivalent of the three words, I don't know. Unwilling to admit of the modifying influence of external agencies on the germ, such theorists resort to the fiction of a spontaneous change. Coleridge somewhere has said "What's gray with age becomes religion." We have toyed so long with this idea of germinal continuity and the invulnerability of the germ, that it has become for some of us well nigh sacrosanct. Living matter is living matter wherever it may be found, but when it happens to be in the germ-cells, verily, "this corruptible has put on incorruption and this mortal immortality"!

Now, no one to-day, qualified by his knowledge of embryology and genetics to the right of an opinion, would, I think, deny that the new organism is in the main the expression of what was in the germ-line, rather than of what it got directly from the body of its parents, but does this fact necessarily carry with it the implication that the germ is insusceptible to modification from without? Is not the serum of organisms with blood or lymph an excellent medium through which external influences may operate upon it? Is it not more reasonable to postulate the origination of germinal changes through some such mechanism as this than to attribute it to mysterious "spontaneous changes"?

With such thoughts in mind I and my research associate, Dr. E. A. Smith, set about making various tests.[2] Without attempting to tell you of our as yet unsuccessful attempts to secure cytolysins which will operate in the developmental stages of such periodically renewed structures as feathers, or to weary you with the history of our various other failures—of which there are an abundance—I wish to speak briefly about certain antenatal effects we secured in rabbits by means of fowl-serum sensitized against rabbit crystalline lens, and of the fact that such induced defects may become heritable.

[2] *Jour. Exp. Zool.*, XXXI, 2, Aug., 1920.

The crystalline lens of the rabbit was selected as antigen, and fowls as the source of the antibodies. The lenses of newly killed rabbits were pulped thoroughly in a mortar and diluted with normal saline solution. About four cubic centimeters of this emulsion was then injected intraperitoneally or intravenously into each of several fowls. Four or five weekly treatments with such lens-emulsions were given. Then a week or ten days after the last injection the blood-serum of one or more of the fowls was used for injection into pregnant rabbits. The rabbits had been so bred as to have the young advanced to about the tenth day of pregnancy, since from the tenth to the thirteenth day seems to be a particularly important period in the development of the lens. It is then growing rapidly and becomes surrounded by a rich vascular network that later disappears. From four to seven cubic centimeters of the sensitized fowl-serum were injected intravenously into the pregnant rabbits at intervals of two or three days for from ten days to two weeks. Several rabbits died from the treatment and many young were killed in utero. Of sixty-one surviving young from mothers thus treated, four had one or both eyes conspicuously defective and five others had eyes which were clearly abnormal. It is possible that still others were more or less affected, since we judged only by obvious, visible effects. We found later in some of the descendants of these individuals that rabbits which passed for normal during their earlier months subsequently manifested traces of defects in their lenses or in other parts of the eye.

The commonest abnormality seen in both the original subjects and in their descendants was partial or complete opacity of the lens, usually accompanied by reduction in size. Other defects were cleft iris, persistent hyaloid artery, bluish or silvery color instead of the characteristic red of the albino eye, microphthalmia and even almost complete disappearance of the eyeball. Taking into account the method of embryological devel-

opment, however—the relation of lens, optic cup and choroid fissure—the defects are probably all attributable to the early injury of the lens. In some cases, both among originals and descendants, an eye microphthalmic at birth may undergo further degeneration such as collapse of the ball and what appears to be a resorption as if some solvent were operating upon it. The eyes of the mothers apparently remained unaffected. This is probably due to the fact that the lens tissue of the adult rabbit is largely avascular and therefore did not come into contact with the injected antibodies.

That the changes in the eyes of the fetuses resulted from the action of lens antibodies is indicated by the fact that in not one of the forty-eight controls obtained from mothers which had been treated with unsensitized fowl-serum or with fowl-serum sensitized to rabbit tissue other than lens, was there evidence of eye-defects, and I may add, that among the hundred or more young obtained later from mothers which were being experimented upon with various types of sera or protein extracts, for other purposes, not a single case of eye-defect has appeared.

As already stated, once the anomaly is secured it may be transmitted to subsequent generations through breeding. So far we have succeeded in passing it to the eighth generation without any other than the original treatment. The imperfection, indeed, tends to become worse in succeeding generations and also to occur in a proportionately greater number of young. Though not analyzed completely as to its exact mode of inheritance, it has in general the characteristics of a Mendelian recessive. Like such anomalies as brachydactyly or polydactyly in man, the transmission is not infrequently of an irregular, unilateral type, sometimes only the right, at others only the left eye showing the defect. In the later generations, probably in some measure as the result of selective breeding, there is an increasing number of young which have both eyes affected.

To determine whether the reappearance of the defect was due merely to the passing on of antibodies or kindred substances from the blood stream of the mother, or to true inheritance, we mated defective-eyed males to normal females from strains of rabbits unrelated to our defective-eyed stock. The first generations produced in this way were invariably normal-eyed, but when females of this generation were mated to defective-eyed males again, we secured defective-eyed young after the manner of an extracted Mendelian recessive. It is obvious that in such cases the abnormality could only have been conveyed through the germ-cells of the male, and that it is, therefore, an example of true inheritance. Subsequent matings have shown that these young transmit the eye-anomalies as effectively as do individuals of the original lines. A new strain of defective-eyed young, established about the time our original paper went to press, is also flourishing and, as regards transmission of the defect, seems to differ in no way from the earlier stock.

But now, let us inquire as to where all this leads. Without entering into a discussion of just what, serologically, is taking place in the body or in the germ of fetuses borne by the lens-treated mothers, the point I wish to emphasize is that a certain specific effect *has* been produced; and, what is of greater moment, once the condition is established it may be not merely transmitted, but inherited. Whether the lens of the uterine young is first changed and then in turn induces a change in the lens-producing antecedents in the germ-cells of these young, or whether the specific antibody simultaneously affects the eyes and the germ-cells of the young is not clear. In any event it is evident that there is some constitutional identity between the substance of the mature organ in question and the material antecedents of such an organ as it exists in the germ.

Biologically considered, the most significant fact is that specific antibodies can induce specific modifications in the germ-cell. Whether these antibodies are trans-

mitted from the mother's blood or engendered in that of the young would seem to be of secondary importance. It stands to reason that antibodies originated in an animal's own body will modify germinal factors if corresponding antibodies introduced from without can accomplish this.

The whole question as to how important such a fact may be in contributing to an understanding of the causes of the germinal changes in organisms in general, which lead to variation and evolution, hinges on the question of whether changes in an animal's tissues will induce the formation of antibodies or kindred active substances in its own body. We have steadily accumulating evidence that such reactions do occur.

In our own laboratory, for example, after many attempts we have succeeded in securing a defective-eyed young rabbit from a mother of normal stock by injecting her repeatedly with pulped rabbit lens before and during pregnancy. Since the young rabbit in question has both eyes badly affected there can be no question that a rabbit can build antibodies against rabbit-tissue which are as effective as those engendered in a foreign species such as the fowl. We have likewise found it relatively easy to secure spermatoxins by directly injecting rabbits, both male and female, with rabbit spermatozoa. Moreover, a given male will develop antibodies against his own spermatozoa if he is injected intravenously with the latter.

We are also securing evidence that serologic reactions induced in the fetus through operations on the mother are not mere passive transmissions, but may become actively participated in by the tissues of the fetus. For example, female rabbits sensitized with typhoid vaccine followed by living typhoid germs may transmit to their young and even to their grand descendants the ability to agglutinate typhoid bacilli in serum diluted from 60 to 160 times. From the standpoint of heredity we have no reason so far for maintaining that this is anything but

placental transmission, though we are going to practice immunization generation after generation for a number of generations to determine if a truly hereditary immunity will be established. However, facts have come to light which show that there is more concerned in the operation than a mere transfer of antibodies from mother to fetus. For instance, the blood of young shortly after birth may show a higher titer than that of the mother. Again, after two or three months of development the young of certain of the sensitized mothers have shown a rather sudden rise in titer, much above that of the mothers. In such cases it would seem that some mechanism in the young rabbit itself is constructing antibodies which supplement those passively derived from the mother. Possibly in the process of development some organ important in such reactions just came into functioning. If this is true further experiments may throw some light on the perplexing question of the source or sources of the antibodies in an animal. After a few weeks, in such cases, the titer drops back again. In still another set of experiments we found that young from a sensitized mother, when nursed by a normal untreated mother, retained a fairly high titer for several months and even showed the rise of titer mentioned. On the other hand, young of an untreated mother when nursed by a sensitized mother acquired a fairly high titer from the milk of the foster mother but lost it rapidly after weaning time. Thus there are evidently constitutional factors operative in the young which have acquired their immunity through the placenta which are absent in the young whose antibodies were conveyed through food.

That changes in the blood serum may be caused by changed conditions in the tissues is further attested by many facts. For example, in pregnancy, the newly forming placenta may set free cells or cell-products which, sometimes at least, cause changes in the blood-serum of the mother, though the exact nature of these changes is

in dispute. Römer, using the complement-fixation technique, found that the serum of adult human beings may possess antibodies for their own lens proteins. Bradley and Sansum, employing anaphylactic reactions, found that guinea-pigs injected with guinea-pig tissue-proteins (liver, heart, muscle, testicle, kidney) develop immunity reactions. Again during the late war, the type of toxic action to which anaphylactic shock conforms was found to exist after extensive injury of the soft tissues. It resulted apparently from the absorption of poisonous substances of tissue origin into the circulation. In fact, various cells and tissues when injured liberate such poisons, and even blood in clotting is known to acquire a transient toxicity of this type.

With facts such as these before us, is it not a rational hypothesis to assume that changes in various parts of a body may on occasion influence the representatives of such parts in the germ-cells borne by that body? This appears all the more probable when we recall the facts learned from the study of precipitins and of anaphylaxis that each species of animal has a thread of fundamental similarity underlying the proteins of all its tissues. There is no reason to suppose that germinal tissue forms an exception. The further fact that homologous tissues, though existing in different species of animals, possess similar chemical characteristics, shows that to get an effect there need not be absolute identity between the protein with which the result is obtained and the original antigen. Since this is so, in order to have a lens antibody affect the germ, there need not be absolute chemical identity between the substance of such a tissue as the lens and the germinal constituents of which it is the expression. And if this is true for lens, why not for other tissues?

The blood-serum of any organism with blood thus affords a means of conveying the effects of changes in a parental organ to the germ-cell which contains the antecedent of such an organ. As long as there is little

change in the somatic element its germinal correlative would presumably remain constant, but any alterations of the soma which give rise to the formation of anti-bodies or other active agents, particularly if long continued, might induce changes in the germ. Such a hypothesis would seem to be plausible at least in accounting for degenerative changes such as the deterioration of eyes in such forms as the mole, or in fact, in the formation of vestigial organs in general.

On the other hand, there is no reason to infer that changes induced in the blood-serum may not also be instrumental in leading to progressive as well as regressive evolution. If we may have germinally destructive constituents engendered in the blood there is no valid reason for supposing that we may not also have constructive ones. When we learn more about what initiates and promotes growth in a part through exercise, or what causes hypertrophy of an organ, we may likewise find how corresponding germinal antecedents of that part may be enhanced. Until such time we shall probably remain in the dark regarding the mechanism of progressive germinal changes. As already indicated, in the hormones and chalones we have a wonderful series of secretions normally circulating in the blood and maintaining general physiological equilibrium. That reciprocal stimulations of various organs occur by this means is a well-established fact. Hypertrophy or atrophy of an endocrine gland may produce pronounced effects in the furthermost reaches of the body. Again we may inquire, is it reasonable to suppose that the germinal tissues will be inviolate to all this ebb and flow of chemical influence? Should we not expect specific reactions or selections here no less surely than in other tissues? Destruction of the pars buccalis of the hypophysis in the frog-tadpole will cause profound alteration in other endocrine organs such as the adrenals and thyroids, will retard the growth rate, render the entire organism albinous, and produce in the individual pigment cells a condition of sustained con-

traction. Shall we conclude that such a far-reaching influence as this, particularly in a developing organism, will pass the germ-cells by unscathed?

Similarly, growth in man is known to be controlled by a pituitary secretion that is carried by the blood to the various organs. The normal development of secondary sexual characters is determined by products from the testes or ovaries, and the activities of the generative organs themselves are intimately associated with the functioning of the adrenal and other glands. The periods of ovulation are inhibited by secretions from the corpus luteum; lactation is incited by products of the corpus luteum, the involuting uterus and the placenta; the carbohydrate metabolism in the liver and even in the most distant muscles is profoundly influenced by substances formed in the pancreas; the pancreas, liver, and intestinal glands are set to secreting through the stimulus of a product formed in the duodenal and jejunal mucosæ. And still others of such remarkable interrelations can be cited.

Truly one may pronounce that social complex of reciprocating individuals termed cells which make up an organism, "members one of another." And with all of these cooperative activities of the various parts of the body it is inconceivable, to me, at least, that the germ-cells, bathed in the same fluid, nourished with the same food, stand wholly apart.

May we not surmise then that as regards inheritance and evolution, Lamarck was not wholly in error when he stressed the importance of use and disuse of a part, or of modifications due to environmental change, in altering the course of the hereditary stream, particularly if we conceive of these influences as being prolonged, possibly over many generations? Have we not in the serological mechanism of the body of animals an adequate means for the incitement of the germinal changes which underly certain aspects of evolution?